UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ACHIM H. KROTZ, and VASULINGA T. RAVIKUMAR

Appeal No. 2005-2380
Application No. 09/032,972

ON BRIEF

Before MILLS, GRIMES, and GREEN, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

VACATUR and REMAND TO THE EXAMINER

On consideration of the record we find this case is not in condition for a decision on appeal. For the reasons that follow, we vacate[1] the pending rejections and remand the application to the examiner to consider the following issues and to take appropriate action.

Claims 1, 6, 9, 10, 27 and 28 read as follows:

1. A method for the preparation of a linear phosphorus-linked oligomer comprising the steps of:

(a) providing a solid support;

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1 Lest there be any misunderstanding, the term "vacate" in this context means to set aside or to void. When the Board vacates an examiner's rejection, the rejection is set aside and no longer exists.

(b) attaching a 5'-O-protected nucleoside to the solid support;

(c) deprotecting the 5'-hydroxyl of the nucleoside with a deprotecting reagent comprising a protic acid in a solvent to deprotect the 5'-hydroxyl of the nucleoside, wherein the solvent consists essentially of an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent;

(d) reacting the deprotected 5'-hydroxyl with an 5'-protected activated phosphorus compound to produce a covalent linkage therebetween;

(e) oxidizing or sulfurizing the covalent linkage to form a phosphodiester, phophorothioate, phosphorodithioate or H-phosphonate linkage;

(f) repeating steps c through e at least once for subsequent couplings of additional activated phosphorus compounds, to produce the completed phosphorus-linked oligomer;and

(g) cleaving the oligomer from the solid support;

wherein steps (b) through (f) are preformed with an automated device;

wherein said oligomer is a linear oligomer.

6. The method of claim 1 wherein the solvent in step (c) is selected from the group consisting of o-xylene, m-xylene, mesitylene, and diphenyl ether.

9. The method of claim 1 wherein the solvent in step (c) is a halogenated aromatic solvent, or halogenated alkyl aromatic solvent.

10. The method of claim 9 wherein the solvent of step (c) is chlorobenzene or benzotrifluoride.

27. The method of claim 21 wherein the solvent in step (c) is a halogenated aromatic solvent, or halogenated alkyl aromatic solvent.

28. The method of claim 27 wherein the solvent of step (c) is chlorobenzene or benzotrifluoride.

The prior art references cited by the examiner are:

Ravikumar	5,705,621	Jan. 6, 1998
Caruthers	4,973,679	Nov. 27, 1990
Froehler	5,548,076	Aug. 20, 1996
Caruthers	4,458,066	July 3, 1984
Caruthers	4,500,707	Feb. 19, 1985
Caruthers	5,132,418	July 21, 1992

Sproat (I), "2-O-Methyloligoribonucleotides: Synthesis and Applications," Ch. 3 in Oligonucleotides and Analogues – A Practical Approach, Eckstein, ed., IRL Press, New York, NY, 1991, pp. 49-86.

Conway, et al., "Site-Specific Attachment of Labels to the DNA Backbone," Ch. 9 in Oligonucleotides and Analogues – A Practical Approach, Eckstein, ed., IRL Press, New York, NY, 1991, pp. 211-239.

Atkinson et al., "Solid-Phase Synthesis of Oligonucleotides by the Phosphite Triester Method," Ch. 3 in Oligonucleotides and Analogues – A Practical Approach, Gait, ed., IRL Press, New York, NY, 1985, pp. 35-81.

Sproat et al. (II), "Solid-Phase Synthesis of Oligodeoxynucleotides by the Phosphotriester Method," Ch. 3 in Oligonucleotides and Analogues – A Practical Approach, Gait, ed., IRL Press, New York, NY, 1985, pp. 83-115.

Horn et al. (Horn 1)[2], "Forks and combs and DNA: the synthesis of branched oligodeoxynucleotides," Nucleic Acids Res., Vol. 17, No. 17, pp. 6959-6968 (1989)

Horn et al. (Horn 2)[3], "Chemical Synthesis and characterization of branched oligodeoxyribonucleotides (BDNA) for use as signal amplifiers in nucleic acid quantification assays," Nucleic Acids Res., Vol. 25, No. 23, pp. 4842-4849 (1997)

Grounds of Rejection

1. Claims 1-42 stand rejected under 35 U.S.C. § 103(a) over Ravikumar in view of Caruthers, Froehler, Sproate I, Conway, Atkinson and Sproat II.

2. Claims 1-42 stand rejected under 35 U.S.C. § 103(a) over Horn 1 and Horn 2.

We vacate each of these rejections and remand the application to the examiner for further consideration of the following matters.

2 Referred to by the Examiner as Horn UA.
3 Referred to by the Examiner as Horn WA.

DISCUSSION

Background

According to the specification, known methods for synthesizing oligonucleotides using intermediates having phosphorus-containing covalent linkages involve the protection of the 5'-hydroxyl group of a nucleoside by forming trityl or substituted trityl or triarylalkyl derivatives. Specification, page 6. The protecting groups are later removed under acidic conditions to yield the free 5'- hydroxyl group and, again, such methods are known. The hydroxyl group can then be further reacted to give a coupled product. Id.

The removal of trityl and other protecting groups is generally carried out in the presence of halogenated solvents such as dichloromethane or dichloroethane. However, the use of such halogenated solvents is undesirable for several reasons, particularly in relatively large scale applications such as the manufacture of oligonucleotides or analogs for use as antisense agents. Id. The claimed invention is indicated to solve this problem by particularly providing a method which includes the step of "c) deprotecting the 5'-hydroxyl of the nucleoside with a deprotecting reagent comprising a protic acid in a solvent to deprotect the 5'-hydroxyl of the nucleoside, wherein the solvent consists essentially of an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent."

The specification further provides that the protic acid "is formic acid, acetic acid, chloroacetic acid, dichloroacetic acid, trichloroacetic acid, trifluoroacetic acid, benzenesulfonic acid, toluenesulfonic acid, or phenylphosphoric acid." Specification, page 10.

In some preferred embodiments of the methods of the invention, the solvent in step (c) is an aromatic solvent, an alkyl aromatic solvent, or an aromatic ether. In more preferred embodiments the solvent in step (c) is benzene, toluene, benzonitrile, o-, m- or p-xylene, mesitylene, or diphenyl ether, with benzene, toluene or o-, m- or p-xylene being more preferred, and toluene being particularly preferred. Specification, page 15.

ISSUES FOR CONSIDERATION

Upon return of the application, the examiner should consider the following:

1. Prior to applying a rejection the examiner should properly interpret the pending claims. Claim 1 step (c) recites a step of, "deprotecting the 5'-hydroxyl of the nucleoside with a deprotecting reagent comprising a protic acid in a solvent to deprotect the 5'-hydroxyl of the nucleoside, wherein the solvent consists essentially of an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent."

For example, with respect to the deprotecting agent, claim 1 uses the open ended language "comprising" a protic acid. The use of the transitional phrase "comprising" itself indicates that the elements or steps following the transition may be supplemented by additional elements or steps and still fall within the scope of the claim. Scanner Technologies Corp. v. ICOS Vision Systems Corp., 365 F.3d 1299, 1303, 70 USPQ2d 1900, 1904 (Fed. Cir. 2004). Thus, claim 1 is open ended with respect to the inclusion of additional components. Claim 1 further requires that the solvent "consists essentially of" a specific group of aromatic solvents. Disclosure relevant to the solvent appears in the specification at pages 6-8 and 15, particularly, page 6. The examiner should determine whether appellants have provided a clear indication in the specification or claims of the basic and novel characteristics of the claimed solvent. If the appellants have not provided a clear indication of the scope of the term "consisting essentially of" with respect to the claimed solvent, the term should be construed as equivalent to "comprising." See, e.g., PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998).

The examiner should determine whether the solvent "consists essentially of" an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent or an aromatic ether solvent, and thus excludes the use of a toluene/CH_2Cl_2 solvent, dichloromethane and dichloroethane. See, specification, page 6.

2. In addition, according to the specification, "modified compounds are included within the definition of the term "'phosphorus linked oligomers.'" Specification, page 13. According to the specification these modifications include, "base modifications, backbone modifications, phosphate modifications, sugar modifications and 2' modifications." Id. See also, Specification, page 28, Example 7. Therefore, while claim 1 describes the preparation of a linear oligomer, the examiner should determine whether claim 1 should be interpreted to read on linear oligomers that may include modifications such as further branching at the 2' position, backbone modifications, etc.

3. Upon return of the application to the examiner, the examiner should consider the relevance of the combination of Ravikumar and Horn 1 and/or Horn 2 to the pending claims. It would reasonably appear the Ravikumar describes each step of the claimed synthesis method, but does not appear to describe the claimed deprotection solvent. Horn 1 and Horn 2 would appear to describe deprotection solvents in the context of oligonucleotide synthesis using trityl protecting groups.

Ravikumar would also reasonably appear to suggest that selection of a protecting group and a deprotection solvent from available solvents is within the skill of one of ordinary skill in the art. In particular, Ravikumar, column 14, lines 5-28, particularly lines 21-24, states that the protecting group, "can be removed from oligomeric compounds of the invention by techniques well known in the art to form the free hydroxyl." Reference is made in Ravikumar to a publication to support this

position, Green and Wuts, Protective Groups in Organic Synthesis, column 14, line 28. Further consideration of this publication may prove of further relevance to the pending claims.

Horn 2 describes oligonucleotide synthesis using standard solid phase chemistry. Horn 2, page 4844, column 1. Horn 2 would appear to describe the attachment of a 5'-protected (tritylated) linear sequence to a solid support. Id. The deprotecting step of the 5'-hydroxyl is performed with pulses of 3% trichloroacetic acid in toluene/CH_2Cl_2. The 5'-hydroxyl is then reacted with phosphoramidite to couple the nucleotides and the steps are repeated for each coupling. Page 4844, column 2. Standard capping, oxidation and cleavage from the solid support steps would appear to be further described, and a clarification of such a disclosure by the examiner should be made on the record.

The examiner should determine whether the claim limitation that "the solvent consists essentially of an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent or an aromatic ether solvent" precludes the use of a toluene/CH_2Cl_2 solvent as described in Horn 2.

Horn 1 is essentially cumulative to the disclosure of Horn 2, but uses a different solvent. Horn 1 is particularly focused on the synthesis of branched oligonucleotides using dimethoxytrityl protection. Horn 1 describes the use of dichloroacetic acid in toluene for the deprotection step in the synthesis scheme. Answer, page 10, Horn 1, page 6965. If the language "consisting essentially of," in the description of the solvent

is interpreted as excluding toluene/CH_2CL_2 as used by Horn 2, the examiner should explore whether if would have been obvious to use the combination of the detritylation method of Horn I in the detritylation method of Ravikumar.

Upon return of the application to the examiner, the examiner should consider the relevance of these publications to the pending claims.

CONCLUSION

Accordingly, we vacate the pending rejections and remand the application to the examiner for further consideration. Upon receipt of the administrative file, we encourage the examiner to take a step back and reconsider the claim scope together with any relevant prior art. If, after having the opportunity to reconsider the record, the examiner finds that a rejection is necessary, the examiner should clearly articulate the

basis for any ground of rejection on the record being careful to insure that every limitation of each claim is accounted for.

VACATED & REMANDED

Demetra J. Mills)
Administrative Patent Judge)
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)
Eric Grimes) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
)
Lora M. Green) INTERFERENCES
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